

Transcutaneous Electrical Stimulation on Mastoid Regions Increased Mean Flow Velocity in Patients with Ischemic Stroke

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Received date: January 19, 2017; Accepted date: January 24, 2017; Published date: January 30, 2017

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Abstract

Background: Transcutaneous electrical stimulation had been proven to modulate nervous system activity, leading to improvements in blood flow and trophism of tissues. Very few studies had focused on the cerebral hemodynamic effects of transcutaneous electrical stimulation on mastoid regions.

Objective: To investigate the cerebral hemodynamic effects of transcutaneous electrical stimulation on mastoid regions in patients with ischemic stroke.

Methods: A total of 40 patients with ischemic stroke were enrolled in this study. Patients were divided into two groups, 20 patients received drugs and transcutaneous electrical stimulation on mastoid regions as an experimental group, while other 20 patients only received drugs as a control group. All patients received 3 weeks of therapeutic intervention. Transcranial Doppler sonography (TCD) was used to detect the mean flow velocity (mFV) values of the anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA) at the baseline and end of therapy. A paired t-test and one-way analysis of variance (ANOVA) with independent samples t test were used to determine the effects of the intervention.

Results: Patients of the experimental group had a higher mFV values than those in the control group at the end of therapy ($p < 0.05$). The mFV values of the experimental group at the end of therapy had more favorable elevation in the ACA, MCA and PCA than those at the baseline ($p < 0.001$). In the control group, the mFV values at the end of therapy were also higher compared to the baseline ($p < 0.001$).

Conclusion: Our findings seemed to demonstrate that transcutaneous electrical stimulation on mastoid regions had significant effects in the improvement of cerebral hemodynamics for patients with ischemic stroke. Transcutaneous electrical stimulation on mastoid regions might be a valuable neuromodulation technique for ischemic stroke. The mechanisms behind this effect needed to be clarified by further investigations.

Keywords: Transcutaneous electrical stimulation; Mastoid; Ischemic stroke; Transcranial Doppler Sonography; Mean flow velocity

Introduction

Ischemic stroke was a major cause of morbidity and mortality in populations. An ischemic stroke was due to the scarcity of cerebral blood supply. The blood supply of brain was compromised but not completely interrupted in the early phase of ischemic stroke [1,2]. Neurons could continue to progress towards infarction and subsequently injure the adjacent viable tissue without sufficient blood. It was important to enhance cerebral blood flow (CBF) at ischemic core and surrounding area of brain tissue in the early stage. Nowadays vasoactive drugs were widely used to expand vessel and increase CBF in these ischemic regions for treating ischemic stroke [3]. The drugs would not only reduce reaction of the sensitivity of cerebral vessel for infarction lesion, but also expand the normal cerebral vessel. Therefore, the efficacy of increasing drug of CBF in ischemic region by adding inner diameter of vessel was limited and the effect was not satisfying.

Until the early 1800s, the discovery of the electric neuronal transmission, transcutaneous electrical stimulation had been widely used in neurological disorders because of its property of satisfactory effects in pain and inflammation, and improving blood flow and trophism [4]. The use of electrical stimulation was in increasing trend. Based on the research of Omar, we speculated that electrical stimulation on mastoid regions could be an effective intervention to improve poststroke outcome [5]. It was known that a number of functionally discrete tissues involving in cerebrovascular homeostasis located behind mastoid regions. To some extent, transcutaneous electrical stimulation on mastoid regions might provide a novel direction of rehabilitation for patients with ischemic stroke. Considering the fact that ischemic stroke had an impaired autonomic regulation of cerebrovascular homeostasis, we hypothesized that transcutaneous electrical stimulation on mastoid regions might be a reasonable procedure to address cerebral blood flow disorder. However, very few studies had focused on the intracranial hemodynamic effects of transcutaneous electrical stimulation on mastoid regions.

This study aimed to investigate the cerebral hemodynamic effects of transcutaneous electrical stimulation on mastoid regions in patients with ischemic stroke. In order to clearly determine the cerebral blood flow response to transcutaneous electrical stimulation on mastoid regions, conventional medication was performed as a control measure. In this study, the hemodynamic effects of transcutaneous electrical stimulation on mastoid regions were examined using transcranial Doppler ultrasonography to measure the mean flow velocity (mFV) values of the anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA), in addition to compare these results with those from a control.

Materials and Methods

Participants

This study was performed in the Department of Rehabilitation Medicine of Jinling Hospital. The experimental protocol was approved by the ethical committee of Jinling Hospital of Nanjing Medical University in accordance with the Declarations of Helsinki revised in 1983. Patients were included in the study if they were two weeks post stroke, less than four weeks from onset with the National Institutes of Health Stroke Scale (NIHSS) score 15, hemiplegia caused by cortical ischemic stroke, the diagnosis of ischemic stroke confirmed by head CT or MRI, 35 to 70 years of age, paralysis on one side of the body, stable signs and symptoms of disease. Patients were excluded who were brain stem or multiple strokes, seizure within the previous 2 weeks, hemorrhage, transient ischemic attack and those with severe cerebral edema, angina, unstable cardiac condition, abnormal high fever, and high blood pressure over 180/100 mmHg.

All patients with ischemic stroke were examined by the same physician with regard to the selection criteria. Initially, 53 patients fulfilled the above criteria. However, 6 patients were unwilling to participate in this study, and 5 patients did not receive transcutaneous electrical stimulation on mastoid regions regularly. A total of 42 patients eventually participated in this study. All participants were instructed about the procedures for the study and signed informed consent agreements written in accordance with the National Health Council before the experiment.

The patients meeting the above criteria were divided into two groups. 22 patients received medicine together with transcutaneous electrical stimulation on mastoid regions served as an experimental group, while other 20 patients only received medicine as a control group. The administration of drugs include fasudil hydrochloride as vasoactive drugs, ganglioside and mecobalamin as brain cell protective agent, aspirin as antiplatelet agent, nifedipine as antihypertensive medication. At the end of the experiment, 2 patients from the experimental group dropped out the study due to personal reasons not related to pain or other discomfort from electrical stimulation. Finally, we analyzed the results for 40 patients with ischemic stroke. Patients from the experimental group were 12 males and 8 females, lesion location were 11 left hemispheres and 9 right hemispheres, at the age between 38 and 70 years, and their disease course was from 15 to 24 days; those whose diabetes, hyperlipidemia or hypertension is 1, 2, 4, respectively. Patients in the control group were 10 males and 10 females, lesion location were 12 left hemispheres and 8 right hemispheres, aging from 39 to 69 years, and their disease course was from 15 to 24 days; those whose diabetes, hyperlipidemia or hypertension is 2, 1, 3, respectively. The ages, gender ratio, lesion location, illness period, NIHSS score, diabetes, hypertension and

hyperlipidemia of the control and experimental groups were similar. Baseline characteristics of all patients are listed in the Table 1.

Variables	Experimental group	Control group	t(F)	p
Age (year)	57.50 ± 8.59	53.90 ± 9.63	1.247	0.220
Gender No. (M/F)	12/ 8	10/ 10	0.404	0.525
Lesion location (L/R)	11/ 9	12/ 8	0.102	0.749
Illness period (day)	19.55 ± 3.03	18.75 ± 3.23	0.808	0.424
Diabetes No.	1	2	0.36	0.548
Hypercholesterolemia No.	2	1	0.36	0.548
Hypertension No.	4	3	0.173	0.677
NIHSS score	25.55 ± 6.24	24.65 ± 6.27	0.455	0.652

Abbreviations: M, male; F, female; L, left hemisphere; R, right hemisphere; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviations.
Data shown as mean ± SD unless otherwise specified.

Table 1: Baseline characteristics of all patients (mean ± SD).

Transcutaneous Electrical Stimulation on mastoid regions

A WF-420 stimulator device was used to conduct electrical stimulation. The device had the capacity to generate different parameters of current including square, sine, rectangular, and triangular wave, and a current output ranged from 0 to 130 microamperes (mA). For this study, we set the output modulation frequency at 80Hz but varied current amplitude between 10 mA and 25 mA by controllers. The device was a portable neuromuscular stimulator and used 2 reusable, self-adhering surface electrodes. Electrodes contained a small amount of water soluble conductive paste. Connect the surface electrodes to the common input of the stimulator device carried in Teflon-insulated stainless steel wire. Controlled by the clinician, the device delivered a train of rectangular electric impulses via surface electrodes. The skin in the mastoid regions of bilateral ears was cleaned with alcohol or dipped in 0.9% saline solution before placing surface electrodes on the skin. Two circle surface electrodes with 5 cm in diameter were used during stimulation sessions. A self-adhering bandage was used to fit over the surface electrodes to ensure continuous contact. After electrode placement, the stimulus intensity was gradually raised in 0.5 mA steps until the patient could first feel a tingling sensation. Secondly, the stimulus intensity was further increased until the patient reported a tugging sensation. Finally, the stimulus intensity was increased until the patient showed that any further increase would become uncomfortable, that was the maximum tolerance level. The maximum stimulus intensity based on the individual's threshold. Such precautions were taken because an abrupt rise in current might result in paralysis of cerebrovascular responsively [6]. Patients were requested to have a regular meal and maintain adequate hydration during all sessions. Electrical stimulation treatment lasted 20 minutes daily, 5 times a week for 3 weeks.

Cerebral blood flow monitoring

Cerebral blood flow was measured from mean blood flow velocity (mFV) using Transcranial Doppler ultrasonography (TCD) technology [7]. A 2 MHz pulsed-wave Doppler probe was used to record cerebral blood flow velocity in the middle cerebral artery (MCA), anterior cerebral artery (ACA) and posterior cerebral artery (PCA) on the surface of the scalp. All parameters were set at ranges suitable for measurement. Patients were in a relaxed supine position during the whole measurement process. The investigator placed the water-soluble acoustic gel onto the examined area, and then gently placed the TCD probe onto the gel without making contact with the patient's skin. Throughout the examination process, the TCD probe remained perpendicular to the skin surface. The position of the TCD probe varied with the examined area. The MCA, ACA and PCA were insonated through the left temporal window. The MCA, ACA and PCA were identified according to anatomical location, depth of insonation, sound and direction of flow, the characteristic spectral waveform, and by compression of the common carotid artery. After a steady state of FV recording, the mFV data was conducted simultaneously from the TCD monitor system. TCD measurement was performed at baseline (before treatment) and after the third week of treatment (end of therapy). The mFV value was expressed in cm/sec. The rater did not know the patients' allocation group during measurement.

Statistical analysis

The statistical analysis was performed with the statistical analysis program IBM SPSS Statistics 20. Data were expressed as means ± standard deviations (SD). A two-sided p value of less than 0.05 was used as the threshold for statistical significance.

The data of the experimental group were compared with those of the control group. A one-way analysis of variance (ANOVA) with

independent samples t test and the Chi-square test were performed to compare differences between the two groups. The mFV values at the baseline were compared to those at the end of therapy in the two groups using paired t-tests with Fisher's least significant difference method. Independent Samples t tests were also used to determine the effects of surface electrical stimulation on mastoid regions for the changes in mFV values.

Results

Table 1 presented the baseline characteristics of all patients. There was no significant difference between the two groups in terms of ages, gender ratio, lesion location, disease course and NIHSS score ($P > 0.05$). Any significant difference between the experimental group and the control group could not be found according to their diabetes, hypertension or hyperlipidemia ($p > 0.05$).

Table 2 presented the changes on the mFV data of both the experimental group and the control group in the ACA, MCA and PCA from the baseline to the end of therapy. Independent Samples t tests showed no significant difference between the experimental group and the control group for the mFV values of ACA, MCA and PCA at the baseline ($p > 0.05$). At the end of therapy, the mFV values of the experimental group were higher compared to the control group in the MCA, ACA, and PCA ($p < 0.05$). Paired t-tests indicated that the mFV values of the experimental group at the end of therapy had more favorable elevation in the ACA, MCA and PCA than those at the baseline ($p < 0.001$). In the control group, compared with the baseline, the elevation of the mFV in ACA, MCA and PCA was also found respectively at the end of therapy ($p < 0.001$).

Group	Treatment	MCA	ACA	PCA
Experimental group (n=20)	Baseline	40.6 ± 3.3	32.7 ± 2.8	24.3 ± 3.4
	End of therapy	52.8 ± 3.6	44.1 ± 3.8	33.8 ± 4.3
	t/p	10.577/2.117E-9	10.135/4.237 E-9	6.992/0.0000117
	t/p ¹	1.591/0.120	1.726/0.093	0.975/0.336
Control group (n=20)	Baseline	42.1 ± 2.9	34.7 ± 4.4	23.2 ± 3.4
	End of therapy	46.9 ± 3.2	39.6 ± 3.1	26.9 ± 4.0
	t/p	4.274/0.00041	4.748/0.00014	3.564/0.00207
	t/p ²	5.489/0.0000286	4.108/0.000204	5.267/0.0000576

Abbreviations: mFV, mean flow velocity; SD, standard deviations; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

Data shown as mean ± SD.

Expressed statistical results between baseline and end of therapy; ¹ showed statistical results between two groups at baseline; ² indicated statistical results between two groups at the end of therapy.

Table 2: Comparisons of the mFV values between the two groups (mean ± SD, cm/sec).

Discussion

In this study, the mean flow velocity response to mastoid stimulation in patients with ischemic stroke was measured by using Transcranial Doppler ultrasonography technique. A increase of the

mFV response to binaural stimulation was found. The results of our study showed that transcutaneous electrical stimulation on mastoid regions resulted in significant improvement of cerebral hemodynamics. TCD was a simple noninvasive tool to assess the cerebral blood flow.

Ischemic stroke was a cerebrovascular disorder causing various symptoms including sensory disturbances, motor weakness, balance problems, and spasticity. Although patients with ischemic stroke received much traditional rehabilitation treatment, the outcome was not satisfying. To address the unsuccesses of traditional interventions, electrical stimulation could represent an alternative or combinatorial strategy for the treatment of ischemic stroke [8,9]. Several evidences indicated that electrical stimulation of various sites of brain could markedly increase its local blood flow [10,11]. This central neurogenic control of the cerebral circulation resulted from excitation of intrinsic pathways to the brain. According to Reis and Latkowski, many functionally discrete tissues involving in cerebrovascular homeostasis such as subthalamic vasodilator, fastigial nucleus, parasympathetic and sympathetic nerves, located behind mastoid regions [12,13]. Mastoid electrical stimulation might be a valuable method for ischemic stroke. This study was designed using TCD to determine whether transcutaneous electrical stimulation on mastoid regions would increase cerebral blood flow for ischemic stroke, and might be similar to the stimulation of the subthalamic vasodilator area and fastigial nucleus, induce neuromodulatory effects on intracranial hemodynamics.

As we introduced in the Transcutaneous Electrical Stimulation on Mastoid Regions Section, special attention in the current study was paid to obtain the cerebral blood flow response. Patients were familiarized with the sensation of stimulation at the beginning of the therapy. Electrodes placement targeted on the mastoidea regions of bilateral ears during stimulation. Such placement of the two electrodes was in order to obtain the transmission of the current throughout the longitudinal axis of brain. The current from surface electrodes passed through the skin, adipose tissue, bony "window" and mastoid foramen, and finally delivered to the intrinsic pathways and tissues surrounding the brain. The stimulus intensity in our research was based on patient's sensation and tolerance. If the patient reported to feel pain or other discomfort, the intensity of current was decreased to the moment when this feeling stopped. We found that electrical current from surface electrodes resulted in markedly increase in mFV values of ACA, MCA and PCA. We concluded that transcutaneous electrical stimulation on mastoid regions, by increasing blood flow in the area surrounding the infarction, would contribute to offset the partial ischemia there and preserve marginally damaged neurons and tissues. In addition, the elevation of cerebral blood flow elicited by such stimulation might also meet the demands for O₂ of the tissue surrounding the infarction. Similar research was recently conducted by Wu, in which electrical stimulation on bilateral mastoid was used to investigate the effect on improving neurological function and intracranial hemodynamics of subacute post-stroke patients [14]. From these results, the hypothesis of cerebral hemodynamic effects of mastoid electrical stimulation could be advanced.

In this context, the cerebral hemodynamic effects of such stimulation were mixed. According to Glickstein, fastigial nucleus (FN) had play an important roles in cerebrovascular regulation. Several studies suggested that electrical stimulation of the FN could markedly elevate rCBF globally in the brain [15,16]. These studies also showed that in many brain regions including the cerebral cortex, the increase in rCBF elicited from FN stimulation was not associated with the changes of local cerebral metabolism. Here the increase in mFV elicited by transcutaneous electrical stimulation on mastoid regions was unknown but might associate with intrinsic circuits and various neuronal elements including subthalamic vasodilator area and fastigial

nucleus, perikarya or axons, which mediated this central neurogenic neuromodulatory.

As mentioned above, non-invasive brain stimulation technique such as tDCS was excellent treatment option. Many studies had shown the efficacy of transcranial direct current stimulation (tDCS) [17,18]. As far as mFV improvement was concerned, our findings in present research were not comparable to the results of tDCS conducted by some authors. Due to the heterogeneous nature of stroke, the number of patients who receive tDCS was limited. The current result added to the increasing evidence that the damage produced by cerebral ischemia might be substantially reduced by transcutaneous electrical stimulation on mastoid regions. However, this effect should be explored further through research.

In contrast to other methods, TCD sonography could record real-time variations in brain circulation. It had been documented that the mFV derived from TCD was widely accepted as index of the primary outcome among cerebral hemodynamics. Although the mFV was not synonymous with actual cerebral blood flow, the changes in mFV correlate with trends of blood flow alteration. The mFV derived from TCD and actual cerebral blood flow was directly or indirectly affected by anesthetic drugs and vasoactive drugs, temperature, PaO₂, PaCO₂, blood viscosity and cerebral metabolism [19]. As the use of electrical stimulation was in increasing trend, knowledge about the cerebrovascular effects would help in the optimal use of this approach with minimal alteration in cerebral hemodynamics.

To our knowledge, there was few study that had examined the effects of transcutaneous electrical stimulation on mastoid regions in patients with ischemic stroke. Preliminary results of our study represented a level of regulation of the cerebral circulation complementary to those mediated by cerebrovascular autoregulation, coupling to metabolism, and autonomic and sensory nerves arising from neurons located outside of the brain. We considered that transcutaneous electrical stimulation on mastoid regions was a promising therapeutic approach for treating ischemic stroke because it was much less invasive and less costly than other approaches.

The mechanism behind this effect was as follows. First, a link between brain and mastoid could be considered to exist through numerous intrinsic loops [20]. Once the mastoid regions was stimulated, activation of the intrinsic pathway might introduce the autoregulation of cerebrovascular homeostasis and the release of vasoactive substance. Second, mastoid electrical stimulation could decrease neuronal excitability at the ischemic surrounding area, and elevate the tolerance of neuron for ischemic damage [21]. Finally, such electrical stimulation could improve the elasticity of cerebral artery, and increase oxygen pressure of cerebral tissue [22]. These reasons might underlie therapeutic benefits associated with the stimulation on mastoid regions.

However, several limitations should be taken into consideration in this study. One limitation was that the sample size was small which might be augment for applying of these results in clinical use. Another limitation was that follow-up TCD studies were not performed in the study. Finally, the mechanisms behind this effect should be explored further through research. Further research based on the use of behavioral and electrophysiological evaluations would be done.

In conclusion, this study investigated the cerebral hemodynamic effects of transcutaneous electrical stimulation on mastoid regions in patients with ischemic stroke using TCD technique. The results provided preliminary evidence of the increase in mFV values of ACA,

MCA and PCA elicited by transcutaneous stimulation on mastoid regions for ischemic stroke treatment. Our findings seemed to demonstrate that transcutaneous electrical stimulation on mastoid regions might be a valuable neuromodulation technique for the treatment of ischemic stroke.

Acknowledgements

The authors were grateful to the participants for their collaboration and wished to express their gratitude to our corporate partners for their assistance.

Ethical Approval

The experiment was performed with patients' consent and ethical approval from the Ethics Committee of Jinling Hospital.

Declaration of Interest

All the authors had no conflicts of interest. No commercial organization had conferred a benefit upon the authors.

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